Presidential Commission
for the Study of Bioethical Issues

TRANSCRIPT

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DR. WAGNER: I believe we are assembled. I'm Jim Wagner. It's my privilege to be serving Emory University as its president. I also am privileged to be the Vice Chair of this President's Commission on the Study of Bioethical Issues. Our chairman, Amy Gutmann, has asked me to convey, uh, regrets, at least for this first day of our meetings. She had something come up on Saturday, uh which obligates her today and requires her attention today, but she'll be flying in I believe this evening to be with us tomorrow.

Um, to make this an official meeting, the eleventh meeting of the President's Commission on the Study of Bioethical Issues, we need to recognize for the record our Commission Executive Director, Lisa Lee. So, Lisa --.

MS. LEE: Good morning.

DR. WAGNER: Good morning. Good to have you here. Yes, and thank you for all the work that you and your staff do. I think also it's probably for the record a good idea to, um, uh, go around the table and very briefly, ask each of the Commissioners to introduce themselves. Um, Raju is paying attention. So, I'll start with Raju.

DR. KUCHERLAPATI: Jim, thank you. Raju Kucherlapati, Harvard Medical School.

DR. ATKINSON: Barbara Atkinson, um, Emeritus from the University of Kansas Medical Center.

DR. NELSON MICHAEL: Nelson Michael, the Walter Reed Army Institute of Research.

DR. GRADY: Christine Grady, NIH Clinical Center.

DR. SULMASY: Dan Sulmasy from the Medical School and the Divinity School here at the University of Chicago. Very pleased to, uh, host the Commission.

DR. FARAHANY: Nita Farahany from Duke University Law School and Institute for Genome Sciences and Policy.

DR. HAUSER: Stephen Hauser, University of California, San Francisco.

DR. ALLEN: Anita Allen, Law School at the University of Pennsylvania and Department of Philosophy.

DR. ARRAS: I'm John Arras, University of Virginia.

MS. ALI: Lonnie Ali, caregiver and advocate for Parkinson's research.

DR. GARZA: Alex Garza, Department of Homeland Security.

DR. WAGNER: Thank you all and Dan, yes thank you for hosting – hosting our meeting. We're going to devote the next two days, uh, to the ethical review of pediatric medical countermeasures research.

Uh, by way of introduction, uh, we should remind ourselves and remind those with us that earlier this year, the Commission received a request from the secretary of HHS, Kathleen Sebelius. The request was to thoroughly review the ethical considerations of conducting medical countermeasures research involving children. We've been asked to consider pediatric medical countermeasures as a topic broadly, as well as specifically consider the anthrax vaccine, which will be used to treat children in an emergency, more specifically.

This is the third meeting we've had on the topic and I look forward to continuing the thorough discussion and considered discussion that we've had of the many complex issues involved. The safety of our children, of course is in our culture paramount and it's important that we have adequate opportunity to engage with experts, the public and one another. Most of today will be devoted to expert presentations and a roundtable discussion will devote the last part of the day and tomorrow to member discussion, as we begin to formulate our conclusions and recommendations to go forward to President Obama and to Secretary Sebelius.

It's also worth taking a moment to explain how it is that we will take comments from the audience if anyone in the audience wishes to, uh, participate. At the registration table coming in, uh, there were comment cards. Also, our staff, uh, who are scattered around the meeting will have cards, uh, these cards with them, and you can approach any of the staff. In fact, yeah, you guys have them in your hands. There you go, great. So, now you know who to – and they all seem to be seated stage right. So, if you have questions, please get one of those cards. The cards then will come forward, uh, to me and we will, uh, work them into our Q&A session as time permits.

So, our first session this morning is on, uh, ethical and practical considerations in 407 reviews it says of pediatric research, uh, 407 referring to a particular section of the Code of Federal Regulations.

DR. WAGNER: And, we begin this morning by asking to – taking a closer look rather of the ethics of pediatrics research that presents more than minimal risk but no prospect of direct benefit to healthy children.

We'll hear first from, uh, Dr. Alan Fleischman and Dr. Fleischman is Clinical Professor of Pediatrics and Clinical Professor of Epidemiology and Population Health at the Albert Einstein College of Medicine in New York. He's an elected Fellow and member of the Board of Directors of the Hastings Center and an elected Fellow of the New York Academy of Medicine. Dr. Fleischman has been appointed to several national committees including the National Human

Research Protections Advisory Committee and the Secretary's Advisory Committee on Human Research Protections Subcommittee on Research Involving Children. He is also a founding member of the New York State Governor's Task Force (clears throat) on Life and the Law and served on that task force for 27 years starting as a mere child. (Laughter) So, we welcome Dr. Fleischman and look forward to your comments.

DR. FLEISCHMAN: Thank you very much Mr. Chairman. It's, uh, a great pleasure and honor to share some of my thoughts about the ethical considerations in conducting clinical trials of the countermeasures in children, particularly related to anthrax vaccine trials.

For over a hundred years, pediatricians have argued that children are unique and that research on adults is rarely sufficient to determine if a treatment will be safe and effective for children. About 40 years ago, two prominent theologians Paul Ramsey and Richard McCormick debated the important question, "May parents consent to enroll their children in more than minimal risk research without the prospect of direct benefit?" These were principled arguments for these two, uh, really learned gentlemen. Ramsey prioritizing the interest of the individual child who lacked the capacity to consent, while McCormick argued for a more communitarian approach trusting that parents could weigh and balance the risks to their child with the benefits of helping others.

This argument set the stage for Congress' National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research who gave us these four important reports. In Research Involving Children, they dealt directly with the question at hand today. They suggested that parents should be permitted to consent to enroll their children in research studies with some risks even without compensating benefits, and they went pretty far. They acknowledged, and this is 1970's arguments, they acknowledged that the exceptional circumstances may arise in which considerable dangers to children or to the community at large might be avoided or prevented by exposing children to research attended by more than minimal risk.

And, they continued with their justification and they spoke directly to the issue at hand. In exceptional circumstances dangers to children or the community resulting from a failure to involve children in research might exceed whatever risk is presented by that research. For instance, the threat of an epidemic that could – that could be offset by developing a safe and effective vaccine might justify research involving risk greater than otherwise acceptable.

This recommendation from the Commission resulted in the federal regulations that we have today that were passed in 1983, particularly the Subpart D section about permissible research in children, and you have reviewed these four categories of permissible research.

Vaccine research has generally been approved and justified under one of the first three categories. Much vaccine research is minimal risk. Some have direct benefit to those children knowing full well that there are diseases that we have eliminated in the childhood population based in vaccination, and others have been more fundamental research in vaccine have been

elevated to the minor increase of minimal risk level and no prospect of direct benefit until one proves efficacy of the vaccine.

The Institute of Medicine took up the question of ethical questions concerning research in children and in the 2004 report, it tried to define some of these difficult to define, um, categories and questions. I'm not going to go through all of their report. I hope that you've had an opportunity to see some of that, um, but, I think relevant to today's discussion, minimal risk must be interpreted in relation to the normal experiences of average, healthy, normal children.

Prospect of direct benefit should be interpreted as a tangible positive outcome, a measurable, cure prevention, relief of pain increase in mobility. And, I think that that, um, report clarified what most IRB's and pediatricians around the country had been interpreting as the pediatric regulations.

And then came minor increase over minimal risk. The most controversial of the regulations that had been recommended by the Commission, but, in fact, I believe it's the most important category for the health of children because it allows fundamental clinical research involving children by allowing children to be placed at some risk, only a little bit above minimal. Minor increment truly is a small amount above minimal but it does allow for no prospect of direct benefit research to occur in children, which has an opportunity.

There are four vectors of risk or harm that I think are important here - duration of the risk or harm, probability, magnitude and reversibility. The higher the magnitude, the greater our concern. The greater likelihood of irreversibility, the greater our concern. And, I think that the Institute of Medicine report made that, um, that suggestion, I think quite well.

And, I'd like to say based on the adverse event literature that I've been able to read and that you've heard concerning the anthrax vaccine, um, that over the last ten years, it could be argued that the level of risk of such a trial would be only a minor increase over minimal, but that's for reasonable people to disagree on and scientists to give us the evidence about. But, yet, I believe that research would not be covered by the 406, minor increase over minimal because of the condition part of that regulation, and all children is not a condition. Even if you have them, you know that all children aren't a condition, as defined in the regulations.

So, we then are faced with the 407 or as the FDA calls it, the 50.54 and, in fact in this case, although we can call it 407 since the regulations are quite symmetrical, this would probably be under the FDA 50.54 regulation because it is a drug.

Um, this category, I believe most reviewers would find the appropriate category to approach such research. And, it can only be approached if there is a serious scientific protocol, and this I think is an extraordinarily important part of the 407 process.

We need a protocol that asks valid questions that can be answered with the numbers of subjects that are proposed with good – what we call power calculations to understand that we get an answer to the question, and allows us to assess the level of risk. We also will need clear consent and assent forms and procedures delineated by the protocol, and we will need to determine what level of risk the reviewers believe is appropriate based on the science of the protocol and the data presented.

We also ought to consider that in the 406 part of the regulations, the minor increase over minimal risk, the regulations say that research must be of "vital importance." Yet, in the 407, we talk about a "reasonable opportunity" to further the understanding of a serious problem. The Institute of Medicine thought the vital importance standard was higher. Now, that may be in the language and you may disagree, but I think that's correct and I think we ought to have vital importance as the 407 standard.

So, what are the principles that we ought to think about? 407 asks us to have sound ethical principles. Well, first we need to minimize risk whatever the level of risk in all opportunities. That's a principle in research with children. We ought to have justice concerns and think about recruiting populations and have recruitment strategies that are fair, equitable and appropriate.

Immediately post-9/11, 2001, we made great efforts in New York to protect the victims and the victims' families from overuse abuse and considerations about patriotism and obligation, which might give undue influence to people who would be asked to be subjects of research, and we were quite concerned about those justice concerns.

Third, one of the classic arguments in pediatric research is we start with adults, we go to consenting adolescents, then, to assenting adolescents and young children, then, toddlers, and finally, infants, so that we learn along the way. We complete the understanding of the work with the older group before we get to the more vulnerable younger group.

407 requires public review and comment and I think that should be serious, it should be real, and it should have real community engagement. And, prospectively, I believe we must create both the pre-event research studies, if we're going to and the post-event research studies, which will add a dramatic impact to everything that we do here.

The assent process for those children will need to be developmentally appropriate, will need to inform the child about the study from the perspective of the child's experience with the study, and will need to clearly elicit willingness from the child, while respecting any reluctance or refusal. This is extraordinarily important in the assent process and rarely is it done in an elegant manner.

So, my conclusions for your consideration. First, we need a scientifically strong protocol, which we could be convinced was of vital importance to the health and welfare of future children. This protocol will not in my opinion, tell us very much about adverse events in children. It'll be too small. But, it will tell us something about dosing, and it will tell us something about the immunogenicity of the vaccine in different doses. Is that of vital importance? The scientists have to make that case.

IRB review must occur and that IRB must agree they think this is important. They wish they could approve it, but they may not either based on the level of risk or the condition. And, therefore, they are asking for the 407, 50.54 review.

We need to make sure that the level of risk as articulated in whatever empirical data we have is just a minor increase over minimal, or just maybe a little bit more but, certainly not substantial risk of death or disability, remembering those four vectors of risk.

We need reasonable recruitment populations and strategies, certainly big cities versus small towns make more sense, but I don't know that, but you may. Um, we need a clear informed consent document and process that's had community review, transparency, clarity. We need an assent process in documents that make sense for children, and we know how to do that. We need to stratify the study so that older children come before the younger. We need a robust public review and comment. And, I believe strongly, we need the pre and post studies to be planned and executed if we're going to go forward with the pre. Thank you very much.

DR. WAGNER: Thank you. We will move now to, uh, Dr. Mary Faith Marshall for her comments before we open for Q&A. And, Dr. Marshall is the director of the program in Biomedical Ethics at the Center for Biomedical Ethics and Humanities at the University of Virginia where she is also serving as Professor of Public Health Sciences in the School of Medicine and Professor of Nursing in the School of Nursing. She's past president of the American Society for Bioethics and Humanities and the American Association for Bioethics. She has served as chair of the National Human Research Protections Advisory Committee and special expert consultant to the Secretary of Health and Human Services on research involving children and prisoners. Welcome, Dr. Marshall.

DR. MARSHALL: Thank you. Thank you very much Mr. Chairman and Commissioners. Uh, this is an august group. Um, fabulous presentation by Dr. Fleischman. I had the benefit of seeing his slides, uh, prior to giving my talk, and I have to say, uh, having looked at all of the materials, um, with which you all have been presented, uh, in the past that it's, uh, it's a bit of a challenge perhaps to -- to say something new.

Uh, so, I'm going to talk about risk. I'm going to talk about children. Um, and, uh, the ethics of research, uh, and clinical medicine in mass casualty medicine. Um, there are some similarities and some important differences.

Uh, so, this is an illustration of the Black Death, uh, by, uh, a Norwegian artist, uh, Theodore Kittelsen. Um, it's entitled, "Plague on the Stairs." Uh, and, the interesting thing about this, the reason that I'm showing it to you is because it's – the perspective is from that of a child, if you look closely at the illustration. And, um, that's, uh, something that I think we're very much concerned with today, uh, the perspective of children, uh, and their interests.

Uh, just to repeat very briefly, um, the slide that Dr. Fleischman showed you, um, this – the important category of exceptional circumstances, um, and issue that failure to involve children, um, in research might exceed, um, whatever risk is presented by that research, and I think this is the challenge with which you are faced. Um, this is the challenge with which subsequent groups, um, IRB's, um, a 407 panel will be faced, um, and I think the difficulty is going to be, um, an assessment of, um, risk in the face of non-perfect information. Uh, so, um, Dr. Fleischman has discussed the – the, um, National Commission guidance that, um, a safe and effective vaccine may occasion, um, a risk greater than otherwise acceptable.

Um, so, I should disclose the fact that I was a student of Joseph Fletcher. Uh, he was a sort of well-known bioethicist and contrarian. Um, it's perhaps appropriate that we're meeting in, um, the building that houses the department of religious studies because many of the sort of leaders and foremost thinkers on ethical issues and research were theologians like Paul Ramsey, uh, like Richard McCormick and Joseph Fletcher.

Um, so, Paul Ramsey actually, uh, said in his work, uh, "The Patient is Person", that to experiment on children in ways that are not related to them as patients is a sanitized form of barbarism. So, strong words. Uh, um, sort of a gauntlet thrown down on the floor. Uh, however, he gave himself, um, an out. This was not an absolutistic stance on his part.

Um, he also said that no parent is morally competent to consent that his child shall be submitted to hazardous or other experiments having no diagnostic or therapeutic significance for this child himself.

Um, the NURPAC was, um, um, brought into being, um, after several unfortunate events that galvanized the attention of the federal government and the Secretary, then, Secretary of Health and Human Services, Donna Shalala. And, one of those was the death of Jesse Gelsinger in a gene transfer experiment at the University of Pennsylvania.

Um, and I think their protocol, some of the perhaps ethics advice that I have critiqued in the past, um, is that they allowed only persons who were 18 years and older to enter the protocol and that wasn't the original design. The original design was for children who had a full-fledged form of a genetic disorder that would result in their death to be research subjects. And, some of the bioethics advice that they received was that parents of children who were dying could not give informed consent to research, um, which, uh, deserves a critique. Um, parents of dying children make clinical decisions and they make research decisions, and that's, um, uh, many of us think that was not well reasoned advice, um, and that parents certainly can and do make difficult decisions in all kinds of circumstances.

Um, so, here was Ramsey's out, recognizing that banning children from non-therapeutic research would leave them without adequate medications and available therapies, he exhorted researchers to 'sin bravely.' So, maybe that might give you a little moral courage here in the, uh, building that houses religious studies that, you too may 'sin bravely', um, if you're thinking, um, along the lines of, um, research – this research that should be approved perhaps under a 407 process. Um, and, he said that the ethically trustworthy investigator, um, should be one who doesn't deny the force – the moral force of the imperative he relates. So, even Ramsey was not absolutistic, uh, about, um, what he defined as non-therapeutic research.

Um, so, this raises the question – the question was raised during the Clinton Administration certainly about ethical issues in pediatric research, the notion of therapeutic orphans, uh, that the majority of therapeutic agents, um, that were on the market that were being given to children had not been tested in children. Um, raised the issue of whether we were being over protectionists in terms of our stance, um, and the federal regulations, um, and thus, harming children as a class.

Um, so, um, the FDA, actually listed ten drugs, um, during that era that were widely used with children that had not been tested, um, and that had no labeling or inadequate labeling, um, for their use in children, and they include for example, the common asthma drug, Albuterol, a drug that I take, Zoloft, Ritalin, Prozac. The interesting, uh, data for me on Prozac is that there were 3,000 doses given to children younger than one year of age.

Um, so very interesting data and it raises the question, how do you assess risks? Um, Dr. Fleischman talked about stratifying the research protocol. You all have sort of heard that, uh, format repeatedly. It's in the regulations. It's, um, sort of conventional wisdom that this is how we approach such problems in pediatric research. I think the problem here or part of it is going to be, ultimately assessing risk in some sort of scientific way. Obviously, those who would present you with a protocol will have to do that. Um, Dr. Fleischman is right, the first and the most important question, um, that should be answered in any protocol is the importance of the scientific question. That's always there. That should be the first thing that's spoken to. Um, so that's going to be, uh, uh, a challenge, uh, for those who are writing pre or post protocols.

Um, so this may – this is, uh, uh, perhaps a not so apt analogy but, I've done a lot of work and thinking about, um, pandemic planning, um, for the State of Minnesota and allocating scarce resources in that context, and, um, allocating resources to pregnant women. Um, an approach to dealing with women who are pregnant during pandemic and thinking about research, um, with this class of persons who also, um, might be defined as, um orphans within the research context.

Um, and so, I've actually suggested and given a copy of a reading, uh, for you all that you might not have expected to see because it is about pregnant women, not children. Uh, it's, uh, written – was uh, written in the Hastings – published in the Hastings Center Report, um, written by Anne Lyerly. Um, and they say in this paper that reasoning well about risk is most challenging when a woman is pregnant for the patient and the doctor alike. During pregnancy we tend to note the risks of medical intervention without adequately noting those of failing to intervene, something that you should sort of, consider here. Yet, when it's time to give birth interventions are seldom questioned even when they don't work. And, outside the clinic advice given to women on how to stay healthy in everyday life can seem capricious and overly cautious.

And, here is sort of the nut, uh, for you all today relative to this article. This kind of reasoning reflects fear, not evidence. You've had a call for evidence uh, from Skip Nelson. You've heard, uh, a call for evidence from Dr. Fleischman. Um, part of my concern about the lack of complete, uh, data about risk has to do with fear and thinking about parental permission, uh, for research, thinking about being a child, um, in the context of an unplanned, um, and frightening event. Um, and whether – how fears plays into, uh, voluntariness, uh, that's a requirement, uh, a prerequisite for informed consent and whether informed consent as a model really even works here.

Um, I want to mention I'm moving closely on time. Um, the work of Griffin Trotter, uh, he has a book, "The Ethics of Coercion in Mass Casualty Medicine". I recommend that to you if you haven't looked at it. He actually has a threat classification, um, that's slightly different than the one Dr. Fleischman mentioned. He talks about his threat classification relative to appropriate

levels of agency. So, federal government intervening and planning, um, for a catastrophic event, or a mass casualty event, um, and justification for coercion. So, we're talking about the research context here, not clinical coercion but, um, there's some important work there. And, his work, I, I, I won't focus too much on it but, it talks about duration, um, of the exposure prior to the effects, uh, and he gives three levels of category there 0-1 hour, an immediate effect, 24 hours, intermediate and greater than 24 hours, prolonged.

Lethality, and I think this is hugely important in the context of anthrax. It has a 75% mortality rate. So, if you were a parent, um, thinking about either a prospective study or, um, a post-event study, um, thinking about, uh, that degree of mortality is important. Um, and he says even a lower, relatively low mortality figure like 10% can cause mass dying when large numbers are affected. This you also heard, uh, from Larry Gostin. And then, how likely is transmission, uh, between others?

So, there are Category A weapons that require federal intervention in terms of planning and research. Uh, and then, there are the third category in which anthrax, um, falls and would perhaps require a federal agency, um, because of its, uh, it, uh, it is different than some of the other, uh, infectious agents, um, and federal assistance relative to anthrax in particular because of stockpiling of, uh, antibiotics or other – or, uh, vaccine laboratory and forensic technology.

So, risk and preparedness, you all have heard from the US National Biodefense Science Board, which supports both pre and post clinical trials, post exposure, um, broad guidance from the National Commission that was just outlined for you by Dr. Fleischman, public discourse and deliberation, which is happening as we speak. Um, and you know that there is disagreement among experts, among pediatricians, among research ethicists, among those who have expertise in disaster preparedness. So, this makes it very difficult. And so, you're probably all saying to yourselves, I'm glad I'm not going to be on the 407 Panel, um, where the paradox really will be assessing the risk of harm to healthy children in the context of uncertainty about risk and there will be uncertainty about risk. Um, so you all, uh, are have this same charge in a sense.

Very quickly, Antinomians Rule. The first 407 Panel, um, is something that I sat on. It wasn't the Dryvax Vaccine Panel. It was a panel that was convened by OHRP. Ernie Prentice, Skip Nelson, Dale Hammerschmidt and I met in Bethesda on a weekend in a basement, um, and we were given three protocols to review. Uh, we didn't review any of them. We, actually, uh, wrote a letter to OHRP about the 407 process and were – had the hubris of defining things like what "serious" means. Um, Dr., uh, Prentice was punished with chairing SACHARP, after that Secretary's Advisory Commission on – Committee on, uh, Human Research and, uh, Dr. Nelson was punished by, uh, being appointed to a fabulous position at the FDA, so that he can advise groups like us. And, I call him many times a year. He's on my speed dial on my phone.

Um, so risk and preparedness. So, what interest – I want to talk about health. So, what interest does a healthy child have in remaining healthy? I think that that's something that you all should consider in your deliberations. I would also like to just maybe occasion a conversation about not only the principle based ethics, um, and autonomy beneficence but perhaps an ethics of care might inform your discussions, and including – included in that would be recognizing the

need that children are parents or children as a class have establishing relationships, being competent within your role as a researcher, um, and the notion of what it means to be a "good" parent. This will be the challenge for parents making decisions about whether, uh, to enroll their children, um, in protocols and what it means to be a good clinical investigator. So, this goes beyond principlism.

Uh, last comment, a couple of comments here. Uh, many institutions, academic research institutions in the country now have, uh, Clinical Translational Sciences Institutes that mandate research ethics consultation. Uh, if the NIH develops a protocol that may be an avenue that it wants to consider. There's a group of experts out there who do consulting on research ethics, um, and it seems to me that's a body -- another body of expertise that might be called upon.

Uh, the 407 Panel will have the benefit, perhaps of information that you don't have today, and that is the benefit of the proposed protocols themselves. Um, the benefit of the informed consent or the proposed consent and assent documents. They will have the benefit of your deliberations. They will have the scientific rationale for a pre-event or a post-event study.

Um, I want to point out and sort of second, uh, an important point that Dr. Fleischman made, um, and that is as you sort of go down the age spectrum, where we can say that a 17-year-old is very much like an 18-year-old, um, not the same with an adolescent and certainly not with an infant. Um, I was sort of thinking back to the dryvax, uh, discussions of children between two and five, and I think that the lethality of – of the anthrax, of the agent here argues for prevention trials and probably post-trials.

So, ultimately, how do you define or know the vaccine is "safe and effective" without doing the research? There lies the rub. Um, and thinking about individual children as collective individuals.

Uh, final slide, uh, pediatrician, uh, William Carlos Williams said, "It's difficult to get the news from poems, yet men die miserably everyday for lack of what is found there." Uh, I think it's a way of saying our ethics inform all of our work including our bench research, and I wish you the best of luck.

DR. WAGNER: Thank you. Thank you both very much. The floor is open for questions and comments. Christine?

DR. GRADY: Thank you both for your testimony. Um, I want to ask a little bit more about risk. So, Alan, you said that perhaps the National Commission was thinking in the 407 category of a minor increment over minimal risk, and maybe even a little more than that.

So, I want to ask you again to say is that – why do you think they thought a little bit more than a minor increment over minimal risk was okay, um, because there are other changes, of course, as you know, from 406 to 407 like condition and stuff like that.

And then, the second question and I'd love to hear Mary Faith's answer on that one too. The second question is related because the National Biodefense Science Board made a statement in their report that said, and I'm going to read it because it's very carefully worded. "The

absence of data about safety and immunogenicity of AVA in children does not support the conclusion that AVA administration presents no more than a minor increase over minimal risk." So, it's sort of a double negative in a certain way. But, the question is really about how do we think about risk because of the absence of data. I mean it seems like a sort of funny twist there.

Um, and then, one last thing, I just want to say. I've seen Alan give a lecture about pediatric research before and I love the symbolic way he describes minimal risk and minor increase over minimal risk. So, I'd love for you to show the group that, your little thing that you do.

DR. FLEISCHMAN: Well, I was considering that but thought I was a little bit –

DR. GRADY: It's very, uh --.

DR. FLEISCHMAN: Silly but, I will do that.

DR. GRADY: Symbolic.

DR. FLEISCHMAN: Uh, I had the pleasure of working with Chris at the NIH, uh, where we teach each year the researchers there and do the child ethics discussion, and I would generally stand at the podium and say, "So, here's risk from zero to a lot, and minor increase over minimal is not at my nose, it's at my thumb and, I would say, the minor increase over minor increase is about the same distance. So that we would double the distance but, we'd still be way over here on the minimal risk side." Now, that's in the eyes of the beholder, um, and I think that's why we need IRB's and we need public discussion to think carefully about that.

I do believe that there are data about risk here. There are no data in children but, we have six million doses, many of whom have been given to young adults. So, I think and I've tried to read some of these articles, I think there's a lot more out there that's not yet been in the published literature that we can benefit from of really parsing that out.

Now, I had my flu shot, because I should, and it hurt like heck for two days. So, if I were filling out an adverse event form, I would say I had an adverse event to the flu shot. It was quite acceptable. It was commensurate with other shots that I've had and that language is in our regulations for children, commensurate, um, and I think it was minimal risk. Um, so, but we do know that of those six million, there were certain numbers of adverse events, and then, there were carefully examined adverse events, and it really came down to a – to an extraordinarily low likelihood of anything that was more than a minor increase over minimal.

Um, but, there is absence of data and that's why I would go down from what we know to what we don't know. Um, but, I would be comfortable in -- in entering into that because I believe the Commission, and I was not there at the Commission. There are people who were there and some may be in the room, um, but I believe the Commission's argument here was

exactly what they said and that was the risk of not knowing is too great. And, I would ask the scientists who write the protocol to convince us of that.

Why do we have to know? We know we have an effective vaccine for adults. Would it increase the risk to infants of having the full adult dose? You know, we intuitively think that if you dilute the vaccine you'll get less risk. Well, I don't know that scientifically. I mean, I would need to be convinced that that was true. Less of the protein would result in less risk. I think so. It's intuitively obvious but it may not be the trigger. The trigger may be the risk and not the dose. So, I need to be convinced.

DR. WAGNER: Did you want to address that, Mary?

DR. MARSHALL: Um, yeah. That was an eloquent response. I guess, you know, I would categorize it, um, in a way as risk creep. Uh, that's, um, that makes sense in the face of the absence of data. Um, and I think that you all, um, and that previous groups have been faced with conflicting information, um, about probability of harm, um, about potential benefit, um, that, you know, may or may not exist to children as a class.

Um, I want to point out that, at least in terms of the dryvax vaccine for the 407 Panel there. That there was, um, in terms of the IRB review leading up to it, um, some institutions that felt that it could live at the 407 level, um, and the institution that moved it forward, uh, was uh, uh, uh, an even split until the chairman of the IRB voted, and it moved forward to the 407 Panel.

Um, the 407 Panel approved the use or the study of the vaccine, which was really about dosing and had already been tested, uh, previously, um, in children, um, was 11 to 0 for the testing.

Um, so very -- sort of very different outcome, uh, from the IRB discussion, um, and the discussion at the 407 Panel. Um, I guess, I would say, um, building on the adverse event, um, commentary that, you know, there will be or should be monitoring and robust data and safety monitoring, uh, even in this small, uh, group, uh, the small end that the study might occasion a pre or post-event study, um, and that you know, um, again an elegant design because of the small end that would be probable in this sort of research. So that's all.

DR. MICHAEL: I'd like to ask you both, um, a question and thank you for your, um, for your testimony, about the bioethics of certain research, um, recruitment strategies that have been, uh, brought up a number of times at, uh, previous meetings on this topic, and I'm going to read to you a statement from – that we received and a public comment from the American Academy of Pediatrics. It said, "As was stated by several speakers during the Commission's two public meetings, we would underscore that parents who have perceived the anthrax vaccine may see great value in enrolling their children in a pre-event study in order to inform the safety and immunogenicity of AVA and children who" – sorry, "children should, uh, an actual anthrax attack occur, it is vital that such research be conducted in accordance with strict, ethical standards."

Now, of course, the vast majority of people that have received the anthrax vaccines are -- are military personnel. So, um, especially based on, on what Dr. Fleischman said about, um, some of the thought process around post-9/11, uh, protocols, I'd like to get your input on whether or not you think that kind of recruitment strategy is reasonable or, if it is intrinsically you have concerns?

DR. FLEISCHMAN: I think it's a question we should ask people who have had the anthrax vaccine. Uh, I've spoken with Dr. Lee about the critical importance of community engagement for you, um, learning from people who are potentially recruited, which would be first responders, military people, people who've had the vaccine.

Um, I don't find that, um, the same as the post-terror impact. I believe that if I were in the military, and I had had the vaccine and I had understood what it was – what it was for, um, I might have a better ability to consent or refuse for my child as long as there was no potential, no potential, for my supervisor to understand I had been asked, not even, whether I said yes or no. I mean I think that's part of the military issue here, and I, you know, I think it's important that we have rules in the military that are like they are, but I worry a great deal about the level of coercion based on, you know, standup and get on line to consent for your children. I don't think anyone should know it, but I do think there is a difference. I think those are reasonable recruitment strategies. I think first responders are reasonable. I think doctors and nurses are reasonable. I think urban-centered people are reasonable of all economic strata. Um, and I -- I would, you know, I would think that we could develop a recruitment strategy that was fair, just and reasonable.

DR. MARSHALL: Yes, I have -- I agree I have concerns. I think, um, there's not only a sort of an issue but perhaps an ethos within the military, and I don't mean that in a critical way but that may, um, occasion a situation or situations where, um, there isn't, uh, as much voluntariness as one might, uh, want.

I think the other important thing is to say, um, and probably this is something where there may be data, um, you should ask for these data, um, of what the prospect for risk is in terms of an event. Um, and is – are members of the military more at risk than members or people who live in urban centers or others. So, so, I'm not persuaded, um, that, uh, I think as certainly, um, that Chairman Gutmann said in her remarks that, um, that that's necessarily a solid plan. I think there are concerns from my perspective about informed consent and voluntariness.

DR. SULMASY: Thanks to both of you for your very helpful comments. I'm going to take us back to risk, which I think is really one of the – the knotty questions we're dealing with and all. You know, start with the questions of the risk of the trial, um, itself. Um, and, um, and say that, um, I appreciate the audiovisuals of the thumbs Alan, but I'm not sure in the end that's really going to help a 407, you know, committee all that much. Um, and I know that it's very difficult to try to come up with, you know, sort of necessary and sufficient conditions, kind of

definition of the risk that we would consider to be a little more than a minor increase (laughter) over minimal risk.

But, perhaps, another way to start on it might be by definition by stipulation saying, "These are the kinds of things that we would consider possibly to be in that kind of a range," um, "And, these are the things that would clearly be beyond it."

This is my first question. Could you help maybe if you can't give us a bright line, um, by stipulation?

And then, the second question, also concerns risk and that's the other issue we're dealing with here is that this is, um, a low likelihood event, when we're thinking about something like, um, anthrax. Um, so we've got, you know, questions about the upper limit of risk for the trial but, we've also got to balance that and some members of the public and Commission have been concerned about the low likelihood of the event of an actual need for any child to have this. And, can you give us some help about, um, how to think about the risk at that end of the spectrum.

DR. WAGNER: And, can I offer a friendly amendment as a third category, the possibility that there are other management tools out there for this, antibiotic management tools?

DR. MARSHALL: So that's certainly – I think the challenge that Dr. Nelson, that Skip Nelson, uh, gave to you, um, and his perspective on, um, on the research is that he needed to see scientific evidence, um, of the reason for at least a pre-event study, um, and that he, uh, had sort of given the fact that antibiotic treatment would work for, you know, sort of the first, uh, event and that, that would allow time for post-event research that he didn't see the necessity of it and that he would need to be convinced of it.

Uh, I don't – I don't have that answer for you but, I think that's the, you know, that's the important challenge and the -- the more data that you might have about, um, from those who may know, uh, Homeland Security or others, um, will give you your best answer. That's – that's the nut of the question right there.

DR. FLEISCHMAN: Well, let me deal with all three of these. First, um, the National Human Research Protections Advisory Committee, uh that Mary Faith chaired and I chaired the subcommittee on children. It's very incestuous here. Um, we came up with a list of suggested procedures that would be called minimal risk and minor increase over minimal risk, as examples. Um, we had not considered at that time what would be a little more than a minor increase of minimal risk but, indeed that's -- reasonable people could disagree on that, and I – I don't, um, you and I probably have a different world view on, on, uh, the need for that kind of stipulation.

Um, I think for me it would be balanced up against what the risk to the class of children was, not the individual child. I think it would be balanced, uh, against the likelihood of a large

number of children being hurt irrevocably, uh, with their death or disability, um, so that your third question fits there for me, too.

So, I might move that line just a little bit, if I really thought that there would be thousands of children dead because of an attack in New York City, um, but I wouldn't move it all the way to a likelihood of death in the trial or a likelihood of disability in the trial but, I certainly would allow for the potential for some pain, a potential for some redness, potential for significant swelling, potential for the child not going to school for a few days. I could see that as possible. And, we always know that with proteins we may have a specific child who has a specific reaction to that protein, and therefore, I would want to setup the trial so that pediatricians and nurses were with those children for a reasonable length of time, so that anaphylaxis was not going to be a problem that couldn't be dealt with even though that's an extraordinarily rare event.

So, I mean I think you can setup those criteria and do that with a reasonable, um, a reasonable, um, a reasonableness.

The likelihood question, well, you know, when we did the – I was not one of the experts on the smallpox vaccine trial but – but, watched carefully as my colleagues looked at that. Um, we knew that smallpox had been eliminated in the world and that if someone was going to use this as a bioterrorist attack, it was going to be a bad person who had stolen it, not made it, not created it but, stole it and it might have gotten out of another country or whatever. So that was our fear but nobody was willing to tell us how likely that was but that was extraordinarily unlikely unless there were extraordinarily bad people who did that, but there were some bad people around.

This is different. My understanding is that anthrax is ubiquitous and good microbiologists or maybe bad people who are microbiologists could, not so difficultly, create this. So, that changes for me the likelihood vector. Even if it's not out there right now, even if we don't anyone who's about to do it, uh, that wouldn't change my view of that question.

And then, about the other measures –

DR. SULMASY: Is likelihood the same as plausibility though?

DR. FLEISCHMAN: Oh, it's very plausible. It's highly plausible.

DR. SULMASY: Yes, it's highly plausible. Does that necessarily increase its likelihood?

DR. FLEISCHMAN: Well, I think so. I think it does. Because if I'm a bad person and it's a plausible thing to do, I can go do it more easily. If it's very hard, then I have to be a better scientist or a better thief or whatever. But, if it's real easy, if it's plausible, then I think it's more likely. So, that – that would be in my calculus.

And then, the question of the antibiotic usage, my understanding is that, um, the antibiotic is quite effective as long as administered very rapidly, um, but that we will not know, um, whether – I mean, we can't give the antibiotics forever and we need to immunize the children just as we need to immunize the adults, so that the spores later on don't cause this fatal disease. I mean I think that science is pretty solid.

Now, do we have to give the immunization the same day as we give the antibiotics? No. But, do we have to give it in the same timeframe? Yes, and my understanding of how we deal with epidemic, uh, issues is if we're going to do it to a million people or hundreds of thousands of people, we better do it at the same time, or we're not going to get the second shot. So, I don't like that word but, the second event to bring the child back for the immunization, uh, because that's going to be a problem. The child is going to be fine. The – the, um, uh, upset level in the community is going to be decreased, and it will be very hard to get that child immunized, I think.

DR. SULMASY: Just quickly to say thank you that was very, um, helpful, at least for me, much more helpful than the thumbs, so thank you.

DR. FLEISCHMAN: Well, I didn't ask to do the thumbs, now. I want to blame Chris for the thumbs.

DR. WAGNER: I'm betting by the time we get through Nita, Raju, Lonnie and John, we'll be up against the time. So let's--

DR. FARAHANY: Uh, so I have a question for Dr. Marshall on two – two things you included on your slides but kind of glossed over in, um, in your talk.

One is you included a quote, uh, I think it was Miller on Ramsey saying that, um, he conflates beneficence with autonomy. Uh, and I was hoping you could expand on that, uh, for what you mean by that and including it and in context here.

DR. MARSHALL: Um, so, it was a way of, you know, I wanted to perhaps, um, most people's perception of Ramsey is that he was sort of an absolutist – absolutist about therapeutic research and non-therapeutic research, and not including children, um, when there was harm. So, I thought it was important, uh, for the commissioners to know that he wasn't absolutistic about that, at all. Um, and that there is a critique of his primary argument, and that is that he conflated autonomy, um, with beneficence and the critique is this. That, um, if the only research that's allowable with children, um, is research where there is – that is therapeutic in the sense that there is a known benefit. Um, then that's the only context in which one allows parents to give permission or consent or assent for their children to be in a study.

So that really it was about – less about um, beneficence then it was making that a condition for autonomy. Um, and then, sort of the notion that, um, children, especially younger

children, um, can never be capable of – infants, of consenting themselves, and so, this notion of parents as proxies has its limitations.

DR. FARAHANY: Great. And, um, there was a second one which is just I was hoping you could expand upon because I thought it was quite a poignant thing to include where you included the statement, "Not to decide is to make a decision." And so, uh, I was hoping you could expand upon why you included that and what kind of caution you're giving us really in including that statement.

DR. MARSHALL: So, that was, um, something that, uh, probably wasn't, didn't originate with him but, something that I learned from Joseph Fletcher. He, you know, said that, um, choice by chance, um, is, um, something that we have to deal with all the time in the sense of, um, thinking about, uh, what is truly, um, random, um, and what's not random. Um, and that, uh, that leaving hard decisions, not that I'm, uh, sort of pointing any fingers or making the critique about any of the bodies that have or will or are considering this, um, but that it's important that when you make difficult decisions that you have, um, the wherewithal and the rationale to back those up. Um, and he was rather, uh, well known for taking, um, what some thought to be, you know, onerous positions.

Um, he and Paul Ramsey, uh, debated vehemently about the criteria for personhood, uh, for example. Um, so – so, it was simply that, you know, sort of stating the obvious, I suppose that, um, you don't have the luxury of not making a decision. That, you know, as I said at the beginning, you're probably all saying to yourselves, I'm glad I'm not on that 407 Panel but, in a sense you are that 407 Panel. Uh, the 407 Panel down the road is going to have the benefit of having more information, having a protocol. So, um, you're at a disadvantage in that respect but, you have to make a decision based on the best information that you have, which is, you know, obviously, a moving target.

DR. FLEISCHMAN: I just wanted to say that actually, Mary Faith, I think this group could preclude there ever being a 407 Panel.

DR. MARSHALL: So, the question is raised if – if there is a way around the regulation, uh, I – you know –

DR. FLEISCHMAN: I just wanted to have said that because I think this -- this could be a decision – I'm not advocating that decision. Um, but I think that it is possible that there could be, um, such a learned argument from this group that it would preclude anyone coming forward with a recommendation to OHRP or FDA.

DR. MARSHALL: I think it's – it's going to need more information than it has right now in the sense of, you know, the good protocol and what the consent document would look like.

DR. FLEISCHMAN: I don't disagree.

DR. MARSHALL: Absolutely, I don't disagree with you either. (Laughter)

DR. FLEISCHMAN: (Laughter)

DR. KUCHERLAPATI: Thank you very much for your comments and presentations today. I want to go back to, uh, a few decades to Ramsey and McCormick and, uh, you know, I don't know them, and, uh, I presume that they're both well recognized ethicists, and, uh, they clearly had very distinct and, uh, diverse views on this subject.

And, the fact that we have, uh, you know, CFR 407 sort of seems to suggest to me that the consensus was that, uh, Ramsey was not right and that McCormick was maybe more reasonable in that if you put adequate protections in everything that you could do this type of research.

The question that I have for you is why did they hold such diverse views? And, I know today that if you deal with the community, they are similar sorts of views that are held today. What's the difference? What is the type of information that one could try to obtain that would actually build a bridge between those two diverse sets of views?

DR. MARSHALL: So, I'm just going to say briefly that I'm not sure that they – they're – that their views were as divergent as we perhaps think they are. I mean, they were on the road together for years, um, debating one another, um, but that's the reason that I gave you the slide where Ramsey gives – you know, "sin boldly" or, you know, "sin carefully" that he would allow for this, and McCormick was really not that far away from that position in the sense that he, you know instead of using Alan's thumb metaphor, you know, he wasn't really that far out there in terms of the amounts of prospective or proposed risk that he would be willing to allow.

DR. FLEISCHMAN: I think this was an evolving argument. Remember that in 1947, the Nuremburg Code said you could never do research in children because you needed consenting adults for research. Uh that scared the pediatric community in terms of how that would impact on children but, we understood why they did that in '47, and in the '70's, I think there were honest, aggressive disagreements. Those debates were spectacular. They were like good prize fighting, um, and they were hard.

Um, and then, the Commission took those arguments and tried to come to some common ground, which is what I think they did. Um, but -- but the public still, I believe wishes to protect its children. We would need to have the public in a large, um, diverse, interactive, um, multiple

community engagement project to understand the question that I think the Commission raises, and that is: what is the risk to children as a class versus the risk to the individual child? And, I will always protect you as a parent and your ability to refuse to allow your child in this study but, do we want to preclude all parents from allowing their child in the study?

So, I think if we did that in the community, uh, we would have a reasonable group that would allow their children in and we respect those in and we respect those who didn't, and we would be able to say to people, uh, that, if it's true that we could protect a large number of children if, in fact this does occur.

MRS. ALI: Thank you both very much. I want to go back a little bit to what Dr. Marshall you talked about you felt that the current model of informed consent may not even work here. Could you expand a little bit about that, uh, on your comment? And then, maybe offer some suggestions about how it should be altered or what should be included?

DR. MARSHALL: Um, so, you know, I think there has been, uh, a debate, really a robust debate in the literature about the adequacy of informed consent or the possibility of such a thing as truly informed consent because in a research context there are always unknowns.

So, you – there are, uh, proposed or perspective benefits perhaps. Um, there are risks, um, that are unknown. Um, risks that are proposed or may be known but, there's always the possibility of unknown risks. Dr. Fleischman referred to that – to that earlier. Um, so – so, I'm not sure, I think informed consent, at least the model that we have of it is based on sort of this principlist approach to doing ethics, um, that we think about benefits, that we think about autonomy, um, people's right to make, you know, independent decisions about whether to enter a trial or not.

Um, whether that model works in a pediatric context, um, sufficiently is a question that I have, which is why I raised, um, the possibility of using a different framework, um, on an additional framework to think about an ethics of care that really talks about, um, what is my, how do I assess need? Um, what is my relationship to individual research subjects or parents who are giving assent or permission to the collective individual in the sense that all children are, you know, at some point, you know, individuals? That we're talking about collective individuals out there and not, sort of like the theoretical, all children, if you will. There's, you know, still individual people.

Um, and that you are competent in terms of what you do, uh, and that you have an ongoing relationship. And, I think that that might work better in the pediatric context. And so, part of that would be, as I mentioned, what does it mean to be a good parent?

Um, so something I learned from my colleague at Children's Hospitals and Clinics in Minnesota, Don Ronquil (phonetic), who is head of their IRB and their bioethics program, he said, often parents have romantic notions about their children and their children's lives. Um, that I'm going to have the perfect baby and that my child is going to be healthy. That the outcome of the pregnancy would be a good and healthy thing, when that's not the truth.

And so, how when your romantic notion is shattered, um, by an -- especially by an event like this, um, does the "good" parent respond? And, I think there are – as Alan said two possibilities or more than one possibility. There's a range of possibilities in saying, I would not let my child do this prospectively or, I see this as enough of a risk that I -- that my definition of being a "good" parent means my duty to protect my child from the risk of harm or for actual harm. And so that's a risk assessment the individual parent would have to make and that, you know, as Alan said reasonable parents and reasonable people would disagree on that. Does that make sense?

DR. FLEISCHMAN: May I just add, um, in terms of the process of informed consent, which is also flawed today and much of our research work, I had the honor of chairing the Federal Advisory Committee to the National Children's Study and being the ethics advisor to that study in which we created a video informed consent for 500,000 potential subjects. Um, so that we knew, it was interactive as well and there were questions of content understanding embedded in that video.

So, we knew that it wouldn't just be that you and I trust each other and you're going to consent for your child because you think I look okay or whatever it is. Um, we had people in that video who looked like the subjects, which means they looked like all Americans in all parts of the country. We had straight language that explained things for people. So, we knew that that informed consent, which was 30 minutes, would in fact, give the same information with the same inflection with the same language to everyone.

And then, we had the people locally who could answer more questions and add but that at least, would guarantee that there would be a uniformity. Not just the language on a piece of paper but of everyone being able to understand in understandable language with clear statements. And then, we actually tested. We didn't call it a test but, we assessed their level of understanding of what they've just been told.

DR. ARRAS: Yeah, uh, thanks guys. Uh, uh, um, I've got a laundry list of things here. One, I just want to follow-up on Nelson's, uh, quote from the American Academy of Pediatrics to the effect that parents would be interested in a study of the safety and efficacy of this vaccine. Correct me if I'm wrong here but my assumption is that this not going to be a study of safety. We're going to get dosing information and immunogenicity information out of this. We're not going to get safety. Is that correct?

DR. FLEISCHMAN: We'll ask the scientists but that's what they've said. Uh, but the – so, therefore, it would be incredibly important if the informed consent didn't allude to that kind of language.

DR. ARRAS: Yeah, (Laughter), yeah I agree completely. Uh, okay, secondly, I want to thank Dan for asking my questions, and I want to thank Alan for answering them, so, so, uh,

astutely. Um, uh, because I – with regard to the need for what you're calling some kind of stipulative definition of what's minimal or what's above minimal or so on. I think we're really sort of hung up in a miasma of abstraction here. You know, it's easy to use the language of minimal risk or more than minimal risk. I've even tried to introduce the language of minor increase over minor increase over minimal risk. Um, and it's also easy I think, it's really quite intuitive, Alan, to use, uh, sort of, uh, yardsticks or hands, you know, to show the magnitude of the risk we're talking about. I tried to float the idea of a yardstick to the staff, but that bombed. Um, but, uh, even that I think is insufficient because what we really need are these stipulative examples of this seems okay but this would go too far. Right? And again, it's also not enough to say, "Oh, we wouldn't, you know, expose children to death or disability," obviously not, but you know, you know, what's in-between? You know, that's the big question for me.

So, then, finally, one, I've got one question that's been bothering me with regard to some language that we're developing in our framework here. What we do essentially is right up on the masthead of our proposed framework for this, right, we've got a kind of Kantian Principle that says you should never treat children merely as a means. Okay. Uh, so, presumably, the rest of the framework is a gloss on that Kantian maxim. The problem that I'm having is that in many – although in many cases, we know a violation of that Kantian maxim when we see it. You know, like if somebody's lying to somebody else or they're stealing their property, you know, they're not treating that individual as a person. Right? As an agent. But, I'm having a lot of trouble connecting up that Kantian maxim with the levels of risks that we're prepared to allow. And, it seems to me that what we're heading toward here is really defining the Kantian maxim in terms of the level of risk that we're proposing to submit children to rather than the other way around. Right? So, I mean, so, I guess my question – I want to turn my puzzlement into a question, which would be is it even worth our while to use this sort of language of never treating children as a means only, and then, just focus on the level of risk that we think is appropriate or prudent for parents to subject their children to.

DR. MARSHALL: I'll respond briefly. I agree with you. Um, if you – one of the references that I have in my slide is this book by, uh, Miller and he makes the same argument. He argues against sort of the Kantian, um, framework, um, in this sort of research. Um, so, children always, also as an end, um, and, you know, you can't promise that in 407 research for an individual child. It doesn't work.

DR. FLEISCHMAN: I agree.

DR. WAGNER: We are really -- Did you want a final word Christine before we – you flagged my –

DR. GRADY: I just have one thing that I've been puzzling over and I've asked many people. Um, we have this sort of and I think both of you actually said it, we have this idea that

the ethnical way to proceed in research with children is to start with the older children and work our way down to the younger children because the older children can consent. But, I'm always struggling with the balance between that and what we're really going to learn. And, in the particular case, I'm wondering, and I've asked many people, couldn't we just skip adolescents because the likelihood of being able to extrapolate immunogenicity data from the adults for the adolescents is pretty high. And, where we might see differences, if there are differences, at all is in the little kids, the young kids. So, what do you think about that?

DR. FLEISCHMAN: Well, I think our pharmacologic colleagues could help a great deal here. I think there is benefit. I would drop the dose rapidly, you know, maybe ten adolescents, and, if you get zero immunogenicity at 25% of the dose that's telling you something. You know, you don't need to do that in the next group and the next group after that. So, I think you can go very small, very fast, and the immunogenicity is really days to weeks. It's not, um, you know, a long time. So, I, think, you know, we've never, at least I don't know. Maybe they have. I mean we've never diluted the dose for adults. Have we? Do we have that data? So, I mean, so, you could rapidly figure that out. That's why I would do it because then you drop out whole levels.

DR. GRADY: And still depend on it.

DR. FLEISCHMAN: Yes, I mean, I think they should consent. I mean consent with their parental consent.

DR. WAGNER: Mary Faith and Alan, thank you so much for stimulating a lot of conversation this morning. We appreciate it you both.

(Applause)